Current Therapeutic Considerations in Osteoarthritis Management

Wendy Gloffke, PhD, ACCP

Learning Objectives
Upon completion of this activity, participants should be able to—

- Identify the multiple factors that contribute to risk of gastrointestinal bleeding, stratify risk of gastrointestinal bleeding in individual patients, and implement practice guidelines that take into consideration the risk of gastrointestinal bleeding when prescribing pharmacologic therapies for patients with osteoarthritis (OA).
- Recognize the basis for and implement the recommendation to exercise caution when prescribing nonsteroidal anti-inflammatory drugs (NSAIDs), inclusive of nonselective and cyclooxygenase (COX)-2 selective agents, for OA patients with risk factors for heart disease; to develop an individualized therapy based on cardiovascular risk while also accounting for gastrointestinal risk and the use of concomitant therapy for cardiovascular prophylaxis or treatment.
- Be aware of and implement the recent recommendations from the Centers for Disease Control/Arthritis Foundation, the Osteoarthritis Research Society International, and the American College of Rheumatology, which include exercise and weight loss if needed in the management of patients with OA, particularly of the knee and hip.

Introduction
The prevalence of osteoarthritis (OA) in the United States has risen rapidly in recent years, and this trend is expected to continue as the elderly population grows. The Centers for Disease Control and Prevention (CDC) reported that OA affected approximately 27 million Americans in 2005, which was an increase from the 21 million reported in 1990. The rates were higher in women than in men, especially among those older than 50 years of age. In order to effectively manage OA, clinicians must be able to recognize factors that influence or complicate treatment options. Recently updated practice guidelines can help inform treatment strategies and clinical decisions, especially in patients who are deemed at risk for gastrointestinal (GI) or cardiovascular (CV) complications with nonsteroidal anti-inflammatory drug (NSAID) therapy.
Mrs. M is a 65-year-old patient who was diagnosed 5 years ago with osteoarthritis of the knee. At her visit today she complains that increasing pain and stiffness in her knee are interfering with her ability to perform daily chores and participate in her normal activities. Mrs. M’s past medical history is significant for diabetes, hypertension, hyperlipidemia, and obesity.

1. Does Mrs. M’s osteoarthritis compound her cardiovascular risk?
   a. Yes
   b. No
   c. Not sure

Cardiovascular Risk and Osteoarthritis
Mrs. M’s OA may increase her CV risk. A 2009 analysis of data from the third National Health and Nutrition Examination Survey (NHANES III) found that, compared with people without OA, people with OA were more likely to have a diagnosis of metabolic syndrome (59% vs 23%) as well as each of the 5 risk factors associated with metabolic syndrome: hypertension (75% vs 38%), abdominal obesity (63% vs 38%), hyperglycemia (30% vs 13%), elevated triglycerides (47% vs 32%), and low high-density lipoprotein cholesterol (44% vs 38%). [4] In another study, OA in any finger joint (a marker for generalized OA) predicted CV death in men. [5]

Mrs. M has been taking the maximum daily dose (4000 mg) of acetaminophen for the last 3 months for her knee pain. Her medication history also includes metformin 500 mg twice daily, glyburide 10 mg daily, lisinopril 10 mg daily, simvastatin 10 mg daily, and baby aspirin 80 mg daily. She asks what you can do to help with her pain.

Gastrointestinal and Cardiovascular Risks and NSAIDs
When acetaminophen is no longer effective for pain management, clinical guidelines recommend NSAIDs, including cyclooxygenase (COX) inhibitors, as the next line of treatment. [6] While these medications are often effective, they are known to be associated with GI and CV side effects, which can limit their use in some patients.

Evidence suggests that most OA patients may be at increased risk for GI and/or CV effects when using NSAIDs. A recent European study (LOGICA) of 3293 patients with OA who required NSAIDs reported that 87% had increased GI risk; 22.3% of those were classified as high risk. The CV risk was high in 44.2% of patients, moderate in 28.5% and low in 27.3%. Overall, 15.5% of patients presented a very high-risk profile, having high GI and CV risks. The type of NSAID prescription was similar regardless of the associated GI and CV risk profile.

www.primaryissues.org
researchers concluded that “Most patients with OA requiring NSAIDs for pain control showed a high prevalence of GI and CV risk factors. Over half of the patients were at either high GI or CV risk, or both, such that the prescription of OA treatments should be very carefully considered.”[7]

You also need to consider that the regular use of NSAIDs may negate the cardioprotective benefits of aspirin. While the evidence is inconclusive, there are enough data to support the cautious use of chronic NSAID therapy.[8-11]

**Risk Stratification**

The risks of adverse GI and CV effects are not equal among all OA patients who use NSAIDs, therefore clinicians should identify patients at risk and assess their level of risk in order to individualize treatment regimens. Their overall risk profile will influence the type, dose, and duration of treatment.[12]

Performance improvement programs also recognize the importance of assessing risk when prescribing NSAIDs in patients with OA. The American Academy of Orthopaedic Surgeons (AAOS) and the Physician Consortium for Performance Improvement®, include NSAID risk assessment in their performance and accountability measurement set for OA.[13]

One approach to risk stratification is to determine which GI and CV risk factors are present (Box 1) and to assign a level of risk (eg, low, moderate, high) to each (Table 1). This risk profile helps determine which clinical guideline recommendations are appropriate for the patient.

<table>
<thead>
<tr>
<th>Box 1. Risk Factors for Gastrointestinal Events in NSAID Users[12]</th>
</tr>
</thead>
<tbody>
<tr>
<td>• History of uncomplicated or complicated GI events (symptomatic or complicated ulcers)</td>
</tr>
<tr>
<td>• Age ≥75 (ACR* ≥65)</td>
</tr>
<tr>
<td>• Steroid use at baseline</td>
</tr>
<tr>
<td>• History of upper GI symptoms</td>
</tr>
<tr>
<td>• Severe rheumatoid arthritis</td>
</tr>
<tr>
<td>• Concomitant use of moderate- and high-affinity serotonin reuptake inhibitors, aspirin, other anticoagulants</td>
</tr>
<tr>
<td>• <em>Helicobacter pylori</em> infection</td>
</tr>
</tbody>
</table>

*ACR = American College of Rheumatology
Risk factors for CV complications in NSAID users can be evaluated using the Framingham method to calculate 10-year risk (Box 2, Table 2).[14] The International Working Party on Gastrointestinal and Cardiovascular Effects of NSAIDs and Anti-Platelet Agents (IWP) criteria for high risk of CV events include established CV disease or an estimated 10-year CV risk greater than 20% in patients without established CV disease.[15] The Framingham Heart Study Web site (hyperlink: http://www.framinghamheartstudy.org/risk/index.html) and the National Cholesterol Education Program Web site (hyperlink: http://hp2010.nhlbihin.net/atpiii/calculator.asp?usertype=prof) offer online tools for calculating CV risk. Cardioprotective factors that influence risk include HDL cholesterol, participation in regular exercise, and moderate alcohol intake.[14]

### Table 1. Risk Stratification for Gastrointestinal Events[22]

<table>
<thead>
<tr>
<th>Risk Factors</th>
<th>Level of Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>None</td>
<td>Low</td>
</tr>
<tr>
<td>1 or 2</td>
<td>Moderate</td>
</tr>
<tr>
<td>3 or more risk factors OR History of ulcer complications OR Receiving concomitant anticoagulants</td>
<td>High</td>
</tr>
</tbody>
</table>

2. How would you describe Mrs. M’s GI risk profile?
   a. High
   b. Moderate
   c. Low
   d. No risk
Treatment Guidelines: Pharmacologic Intervention

The challenge in managing OA in patients like Mrs. M, who may have both GI and CV risk factors, is deciding which medications will provide the greatest symptom relief with the fewest adverse effects. Currently, most practice recommendations state that NSAIDs should be used at the lowest effective dose for the shortest time necessary; long-term use should be avoided if possible.

Guidelines from the American Heart Association (AHA) and the Osteoarthritis Research Society International (OARSI) recommend that in patients with CV risk, NSAIDs and COX-2 inhibitors should be prescribed with caution. [16,17] In patients

www.primaryissues.org
with GI risks, OARSI recommendations state: “In patients with GI risk, either a COX-2 selective agent or a nonselective NSAID with co-prescription of a proton pump inhibitor (PPI) or misoprostol for gastroprotection may be considered, but NSAIDs, including both nonselective and COX-2 selective agents, should be used with caution in patients with CV risk factors.”[17] The American College of Gastroenterology practice guidelines also offer recommendations to prevent upper-GI NSAID-related ulcers based upon 6 risk categories of relative CV/GI risk (CV: high/low; GI: high/moderate/low)[18] (Figure 1).

Table 3 summarizes treatment recommendations for different GI and CV risk levels and combinations.
### Table 3. Summary of Treatment Recommendations for Patients With GI, CV, or Combined Risk Factors

<table>
<thead>
<tr>
<th>Guidelines</th>
<th>CV Risk</th>
<th>GI Risk</th>
<th>CV and GI Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>AHA</td>
<td>NSAIDs and COX-2 inhibitors should be prescribed with caution. COX-2 inhibitors should be prescribed only when no appropriate alternatives are available; prescribe at lowest effective dose for shortest duration necessary.</td>
<td></td>
<td>History of GI event and high CV risk; nonselective NSAIDs and COX-2 inhibitors are not appropriate; consider other treatments. IWP: Naproxen plus PPI or misoprostol can be considered in patients whose CV risk can be considered in patients whose CV risk outweighs GI risk.</td>
</tr>
<tr>
<td>IWP</td>
<td>Patients with high CV risk should receive naproxen; COX-2 inhibitors are inappropriate.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>OARSI</td>
<td>NSAIDs and COX-2 inhibitors should be prescribed with caution.</td>
<td>Either a COX-2 selective agent or a nonselective NSAID with co-prescription of a PPI or misoprostol for gastroprotection may be considered, but NSAIDs, including both nonselective and COX-2 selective agents, should be used with caution in patients with CV risk factors.</td>
<td></td>
</tr>
<tr>
<td>ACG*</td>
<td>Patients with high CV risk and low GI risk should receive naproxen; COX-2 inhibitors are inappropriate. Patients are high CV risk and moderate GI risk should receive naproxen; plus PPI or misoprostol.</td>
<td>In patients with a history of GI event and high CV risk; nonselective NSAIDs and COX-2 inhibitors are not appropriate; consider other treatments.</td>
<td></td>
</tr>
</tbody>
</table>

*Adapted from Schelmen JCI*

*In addition to patients with obvious high risk factors (eg, previous MI, ACS, etc) the ACG guidelines also classify anyone requiring low-dose aspirin for prevention of serious CV events as having a high CV risk.*

---

*Current guidelines recommend that clinicians should individualize therapy and balance CV and GI risk and the use of concomitant therapy for CV prophylaxis or treatment in patients with OA. Clinicians should exercise caution when prescribing NSAIDs, inclusive of nonselective and COX-2 selective agents, for OA patients with risk factors for heart disease.*
Treatment Guidelines: Exercise Recommendations

The CDC and Arthritis Foundation 2010 OA Public Health Agenda (hyperlink: http://www.cdc.gov/arthritis/docs/OAAgenda.pdf) makes recommendations about exercise and weight management in people with OA.[19] They recommend that “low impact, moderate intensity aerobic physical activity and muscle strengthening exercise should be promoted widely as a public health intervention for adults with OA of the hip and/or knee.”[19] They also recommend that “Weight management should be promoted for the prevention and
treatment of OA, and national nutrition and dietary guidelines for the general population should be followed by adults with OA so they select a quality diet while staying within their calorie requirements.”[19] The 2009 American College of Rheumatology (ACR) draft updated guidelines for patients with symptomatic knee OA that is uncomplicated by comorbidities strongly recommend aerobic land-based exercise, resistance land-based exercise, aquatic exercise, and weight loss. The ACR panel did not recommend balance exercises, Tai Chi, lateral wedged insoles for varus knee OA, manual therapy alone, bracing in combination with medical management, or laterally directed patellar taping.[20]

Each additional 10 pounds increases the force on Mrs. M’s knee by 30 to 60 pounds with each step. Mrs. M’s situation is typical among people with OA who would benefit from participating in regular exercise, but who find it too painful to exercise. Advise her that exercise is important for both her weight and her OA. Mrs. M might benefit from referral to a nutritionist or dietitian for help with her weight. She will need to start any exercise program slowly, engaging in safe, low impact activities such as aquatics, walking, or riding a stationary bike. She might benefit from a light resistance training program to increase her muscle strength, followed by nonweight bearing activities such as those mentioned above. Increases in resistance should be made gradually and should not exacerbate her discomfort. Engaging in any of these activities on a regular basis will strengthen her muscles overall, and specifically strengthen the muscles around her affected knee. This in turn will help to stabilize and protect her knee joint. With regular exercise, her ability to function should improve and she should have less pain. Stress that she should avoid any exercise that could potentially injure her knees (eg, skiing).

**Summary**

Mrs. M represents a typical OA patient. She is middle aged, overweight, with complicating comorbidities; acetaminophen is no longer sufficient to manage her pain. As her clinician, you can work with her to develop an appropriate exercise regimen, and establish reasonable expectations for her if she engages in a regular weight management program. Her pain may improve with exercise. Managing her OA pain is complicated and requires that you evaluate her risk for GI and CV events, and consider her comorbidity profile, in order to prescribe the most effective medication with the least amount of risk.
References